AMERICAN JOURNAL OF PHARMACY

and

THE SCIENCES SUPPORTING PUBLIC HEALTH

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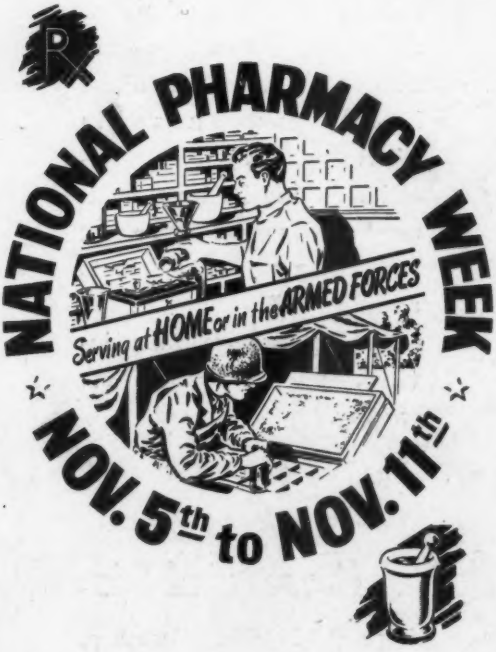

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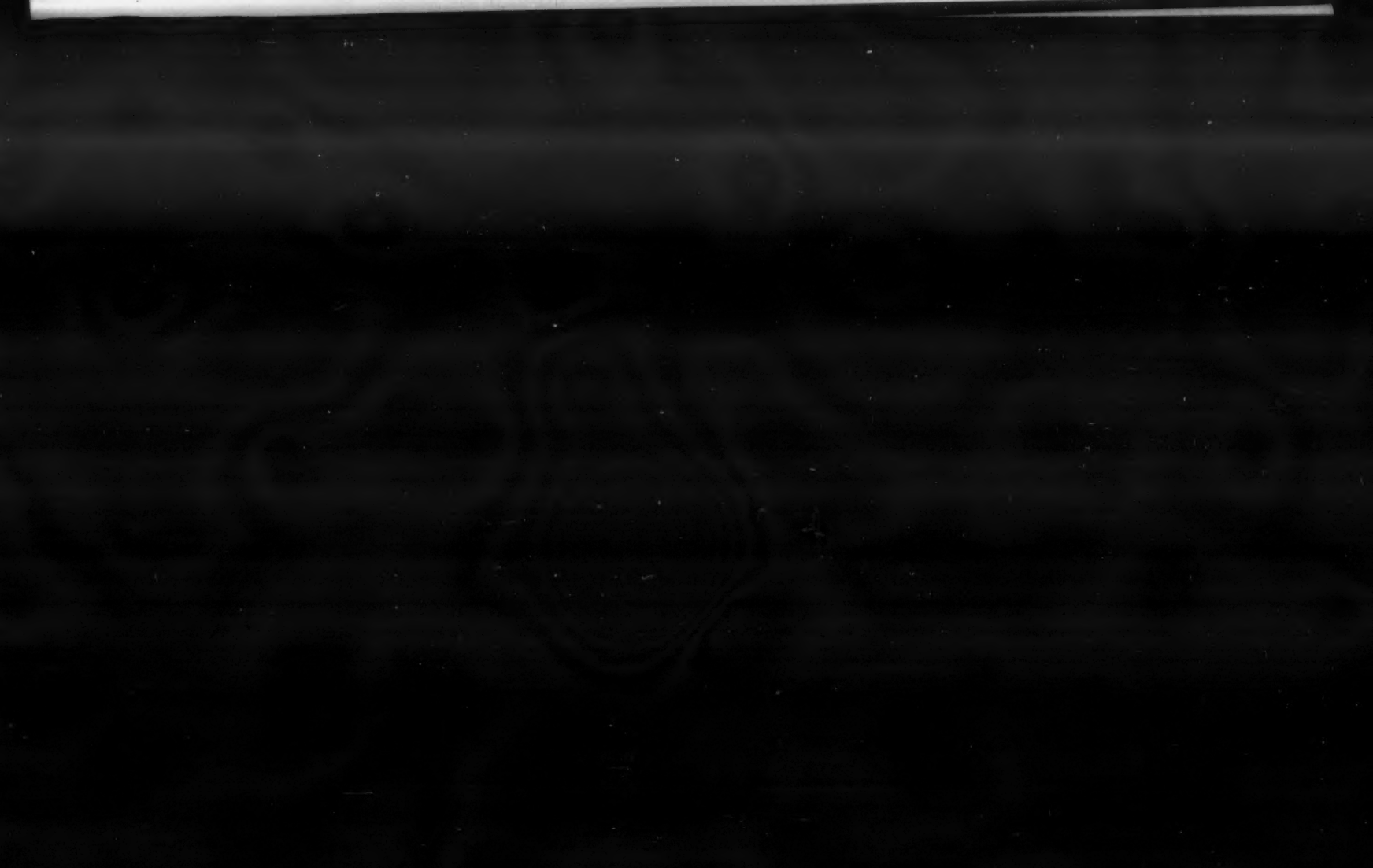

ACME

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He might be a pharmacist from Waukegan or New York, from Stroudsburg or San Francisco. He wears the Caduceus—the emblem with serpents twined around the winged staff of Mercury. In this war, as in other wars, he carries no firearms. But, he certainly carries weapons: the fine ideal of service above self, excellent knowledge of war medicine and the skill to apply it. He is tough and tender—fighting mad, yet calm enough in the thickest of battle to safeguard the lives of his buddies.

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A tribute to the members of the

U. S. ARMY MEDICAL DEPARTMENT

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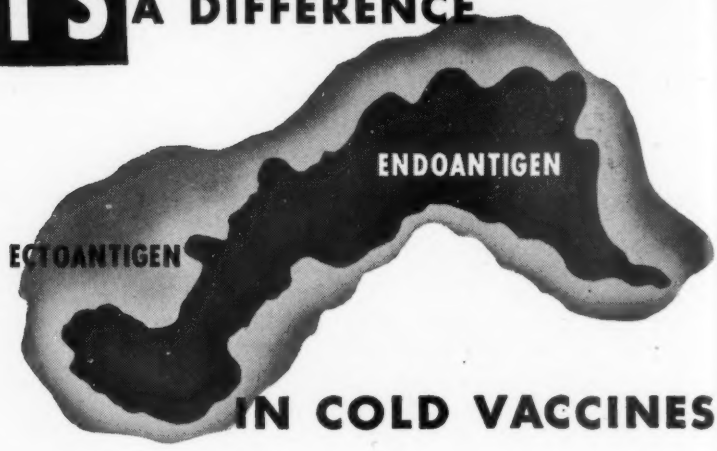

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E D I T O R I A L S

THE AMERICAN SOCIETY OF HOSPITAL PHARMACISTS

TOGETHER with the American College of Apothecaries the American Society of Hospital Pharmacists constitutes one of the most progressive movements within organized pharmacy that has taken place in the last decade. The former is a group composed primarily of practitioners of pharmacy in its professional aspects outside the hospital environment and the latter of men and women engaged as pharmacists on the staff of a hospital. Although the Sections of the American Pharmaceutical Association devoted to meetings of these two groups have been held only a very few years, they already have the reputation of presenting excellent programs to an enthusiastic group which numbers even more than those attending some of the older sections of the A. Ph. A. This issue of the journal contains a paper read before the hospital group by one of our contemporary pharmaceutical journalists.

It is only proper that hospital pharmacists should have organized a professional group within themselves. There is no subdivision in American pharmacy that has more serious problems or a greater challenge. That the hospital pharmacists realize this one can quickly appreciate by talking to almost any one so engaged. The difficulty faced by leaders in this movement is rather getting their organization so geared that these problems can be effectively met.

Hospital pharmacy has changed and is still rapidly changing from a relatively unimportant phase of pharmaceutical endeavor to one of the most, if not *the* most, important aspects of pharmacy. With the current trend to the group practice of medicine, the growth of health

insurance plans, and the medical care to be provided war veterans, it may well be that in time more drugs will be dispensed by hospital pharmacists than by retail pharmacists. Reactionary opinion may scoff at this statement but it is by many considered to be an inevitable and even a progressive step toward improving both public health as well as the profession of pharmacy.

Hospital pharmacists have sensed this growing importance and, like America during its early development, great stresses and strains have appeared, due largely to the fact that growth is taking place so rapidly. Two major problems may be recognized and they are being resolutely attacked by hospital pharmacists themselves. First the technical knowledge and skill of this group must keep abreast not only of progress in pharmacy but of hospital pharmacy's increasing importance. The organization of which we are writing is evidence that this need is recognized. Second, hospital management must be made to see that the pharmacist is a professional person and not just a paid employee; that when this fact is properly recognized and such a status is given, the pharmacist, the hospital, the related professions and the public, all are benefited. This last problem requires the whole-hearted support of every pharmacist and friend of pharmacy regardless of his sphere of activity or interest. Such support should stem not solely from a desire to be helpful but from the realization that, since hospital pharmacy is destined to become an activity of first magnitude, should it develop on other than a sound basis the whole body of pharmacy will suffer, including all its practitioners. We commend the American Society of Hospital Pharmacists and offer it our support in its earnest endeavors.

L. F. Tice.

NATIONAL PHARMACY WEEK

OUR cover this month carries the official illustration supplied by the American Pharmaceutical Association, calling attention to this annual observance of pharmacy's importance in our national life. Its theme, "Serving at Home or in the Armed Forces," is aptly chosen, inasmuch as pharmacy's record during this critical period compares favorably with any activity one might mention. While the implementation of the Pharmacy Corps Bill has not met the expectations of many, it is gratifying to know that pharmacists are in the Armed Forces serving loyally and energetically, both professionally and otherwise. With civilian ranks sharply curtailed by the needs of the Armed Forces and drug needs skyrocketed into almost unbelievable quantities, all essential needs and services have been met adequately and with the least public inconvenience and difficulty found in any comparable field. The manufacturers have received their "E Awards," the soldiers and sailors their medals; let us not forget the harried retail pharmacist who, too, has rendered loyal service with no small effort.

L. F. TICE.

TRENDS IN MODERN MEDICINALS

By Madeline Oxford Holland, D. Sc.*

THE year 1944 has witnessed to date a number of striking advances in therapeutics. Many of these have represented major contributions to chemotherapy, to endocrinology, and to the *materia medica* with which the physician and the pharmacist jointly work to preserve and prolong human life. Equally important, however, have been the developments in pharmaceutical knowledge and technic which have accompanied them.

It is a problem to attempt to include even the most important of such developments in the space of the few pages of this review. It must result in over-simplification, and the omission of many interesting subjects. However, certain of the more important and more promising discoveries and improvements can be selected as properly indicating present trends in modern medicinals.

Most significant of these trends is the lessened importance of the vitamins. These food catalysts and metabolic agents have provided no great advances in the past twelve months. On the contrary, they have assumed the role of standard therapy. More striking than any other development has been the trend in medical thought toward chemotherapeutic agents, in both the field of synthetics and microbiologic agents.

The impact of War, manpower shortage and emphasis on production have seriously curtailed many fields of scientific research, particularly those which have no direct military significance. In the field of military medicine, however, considerable profitable emphasis has been placed on research. Now that some of the discoveries which have resulted have been removed from the realm of military secrecy, they are being announced to the profession and released for civilian use.

The most important group of newer therapeutic agents is, without question, the microbiotics. In many respects they have amply borne out the early extravagant predictions concerning their value.

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* Managing Editor, "American Professional Pharmacist"; Associate Editor, "El Farmaceutico"; and member of the Staff, Philadelphia College of Pharmacy and Science.

Penicillin

In reference to penicillin, new information appears with each passing day. When this new and potent drug was first supplied in commercial package, it was the general impression that penicillin solutions deteriorated rapidly, except when kept under 5° C. This belief developed as a result of experiments with the early, fairly crude preparations. In July as a result of studies conducted by Kirby under actual conditions of clinical use, it was shown that solutions of current commercial preparations of the sodium salt maintained their full potency for a minimum of 7 days at room temperature, and even for 4 days in the incubator. From this it is indicated that one or two days' supply can be mixed and left at the patient's bedside without danger of deterioration. It is believed that this is due to the greater purity of present products, for the marketed penicillin has increased in potency from about 100 Oxford units per mgm. a year ago to over 1000 units per mgm. today. The pure crystalline penicillin (not yet available) is entirely stable under all conditions. This factor is of importance now, but will be more significant when penicillin is once released for general use. It will enable the general practitioner to employ the drug with greater ease in the home. In temperate climates, even in the summer season, he can mix 2 or 3 days' supply, either for intermittent intramuscular injection or for continuous intravenous use, and leave it at the bedside.

Other investigators are experimenting with penicillin as an inhalant, with promising results reported on the basis of preliminary work. It has also been suggested as of possible value as an air disinfectant, sprayed in the form of aerosols.

Another startling concept in penicillin therapy was recently reported by Beyer and colleagues. One of the greatest problems in the administration of penicillin has been its rapid excretion and disappearance from the bloodstream within a few hours after administration. This necessitates almost continuous or frequently repeated administration. The investigators reasoned that penicillin must be eliminated from the blood stream by the kidney tubules, in addition to the kidney glomeruli. Knowing that the nontoxic compound, para-aminohippuric acid, is excreted by the tubules, these workers decided "to determine whether such a mutual competition between penicillin and para-aminohippuric acid existed and, if so, to evaluate the significance of that relationship."

Penicillin and para-aminohippuric acid were administered to test animals in experimental investigations. It was found that the concentration of penicillin in the blood was maintained at a higher level and for a much longer period of time when para-aminohippuric acid was administered. When penicillin was infused at the same rate to two groups of animals, the blood stream concentration of penicillin in those receiving para-aminohippuric acid was four to five times that of the animals not receiving it.

According to the investigators, "these results indicate that with the aid of para-aminohippuric acid one may attain and maintain materially higher concentrations of penicillin in plasma than is practicable without the use of excessive amounts of penicillin." This indicates that possibly penicillin may be conserved and lesser quantities required in the future to accomplish results now requiring large amounts of the drug. Consequently, present facilities for the production of penicillin may prove adequate for civilian needs as well as for those of our Armed Forces. Furthermore, the ability to maintain very high concentrations of penicillin in the blood may find this drug of value in the treatment of disease conditions for which it can not now be satisfactorily employed.

Clavacin

The field of microbiotics is not restricted to penicillin alone even though it has received the greatest publicity. Scientific investigations in recent months have been so intensively focused upon this subject that as a result various other valuable agents have been extracted and tested.

Clavacin, a derivative of *Aspergillus clavatus* (and identical with patulin from *Penicillium patulum*), is believed to be anhydro-3-hydroxymethylene-tetrahydro-γ-2-pyrone-2-carboxylic acid. It apparently possesses a high degree of toxicity, which precludes its use by parenteral administration.

However, further research may discover a solution to this problem. In the interim clavacin may be of value topically in certain skin diseases where the dermal surface is unbroken or where it is applied on the mucosa. If of value when employed in this manner, the newer agent would release increased supplies of penicillin for parenteral therapy. Clavacin has some effect as a fungicide, and is especially active against the colon-aerogenes group as well as for inhibition of

others of the gram-negative type. It has also bacteriostatic and bactericidal properties. In addition, patulin is relatively stable, at least more so than is penicillin. The filtrates may be handled without sterile precautions and aqueous solutions may be boiled without loss of activity. Clavacin (or patulin) is able as well to exist in solutions of high acidity. A final advantage is that patulin can be obtained in amounts of 1 gm. per liter of filtrate, from cultures of certain potent strains.

Streptothricin and Streptomycin

Streptothricin, a derivative of a soil organism, *Actinomyces lavendulae,* has been found to me markedly effective *in vitro* and *in vivo* against many gram-positive and gram-negative organisms and particularly gram-negative rods. It has a greater effect parenterally than orally, but when administered orally it reduces the lactose-fermenting bacteria of the intestinal tract. Because of this property, which is similar to that of certain sulfonamides, it has been suggested that streptothricin may be of value in bacillary dysentery and typhoid fever. The crude drug may prove of value in infected wounds and burns, as it has a marked effect *in vitro* against gram-negative and gram-positive organisms, and it is not inhibited by body fluids.

The action of streptothricin upon certain gram-positive bacteria (such as *Bacillus mycoides*), and upon some gram-negative bacteria (such as *Pseudomonas fluorescens, Ps. aeruginosa, Proteus vulgaris* and *Serratia marcescens*) is, however, rather limited.

Another antibiotic agent, streptomycin, was recently isolated. This agent has an effect upon these organisms as well as being of value against certain other organisms not subject to streptothricin therapy. In other respects streptomycin resembles streptothricin. When tested against *Salmonella schottmülleri, Pseudomonas aeruginosa, Shigella gallinarum, Brucella abortus* and *Proteus vulgaris* promising results were obtained.

However, the search for newer chemotherapeutic agents has been continuing at an increased tempo as well among organic chemists. Recently several new and promising chemical agents have been introduced, most of which are as yet unavailable for general civilian use. When their potency is proven and their safety assured, they will be released, and pharmacists should be fully aware of their value in advance of release.

Diasone, Promin, Promizole

The value of the sulfone group of chemotherapeutic drugs has become increasingly apparent, particularly in the treatment of heretofore-resistant conditions, such as tuberculosis and leprosy. Pharmacists may possibly find drugs of this type in their armamentarium of *materia medica* in the early future, but the sulfone drugs should not be confused with the sulfonamides.

It is noteworthy that by development of a synthetic organic in the sulfone group, based upon the original sulfoxylate improvement of arsphenamine, it is possible that an entirely new group of bacterial infections may be successfully treated.

Diasone, known chemically as the disodium formaldehyde sulfoxylate diaminodiphenylsulfone, is believed to have some value in tuberculosis. It is also considered as a superior chemotherapeutic agent on the basis of its low toxicity. For this reason it can be administered for long periods of time without danger to patients under treatment for those conditions for which it is indicated.

There has already been accumulated an extensive background of laboratory research, but as present no claims are being made concerning it full value. The final answer concerning its therapeutic and physiologic action is not as yet available.

It can be dispensed in capsules, or stored in tightly stoppered bottles, if 10 per cent of sodium bicarbonate has been added to the powdered drug.

Promin is the only other chemotherapeutic drug which is reasonably comparable. It is very soluble and quite active, but has been reported as highly toxic. When employed in the treatment of 200 tubercular patients at the Mayo Clinic, severe reactions occurred.

Promizole, another member of the sulfone group, chemically is 4,2′-diaminophenyl-5′-thiazolesulfone. This drug is less toxic to animals and humans in therapeutic doses than are promin and diasone. It can be administered orally in capsules, or in suspension in water or fruit juices. It has shown little hemotoxic properties, contrasting considerably with those of promin and diasone. Systemic symptoms are slight, with no fever, leukopenia, hematuria or evidence of renal damage. The clinical use of this drug in tuberculosis has given promising results, but further evidence must be accumulated before it is released or before claims for its value may be properly advanced.

The sulfonamides are similarly being investigated in search for newer and more valuable agents. A recent development has revealed the following compound which has particular importance in veterinary medicine.

Phthalylsulfathiazole

Another new sulfonamide not as yet approved for release is phthalylsulfathiazole. Chemically it is 2-(N_4-phthalyl-sulfanilamido)-thiazole or a dicarboxylic acid derivative of sulfathiazole. It is a white or faintly yellowish-white, crystalline powder, odorless and with a slightly bitter taste. It is very slightly soluble in water and slightly soluble in alcohol, but very soluble in warm aqueous solutions of sodium bicarbonate. It has a low toxicity, due probably to the very low concentration produced in the blood and other tissues. All but small amounts of the drug are retained in the gastro-intestinal tract and that which is absorbed is rapidly excreted by the kidneys.

Phthalysulfathiazole is an intestinal antiseptic for veterinary use. It has from 2 to 4 times the bacteriostatic activity of succinylsulfathiazole in the intestine. Administered orally, it has also been effective in the presence of a persistent watery diarrhea.

Topical Administration of Sulfonamides

Developments in therapy naturally have involved improvement in modes of administration, as well as in the development of new drugs. The topical administration of sulfonamides has been the subject of much discussion during the past year. These drugs have been found exceedingly effective in the local treatment of impetigo, ecthyma, chancroidal infection and acute pyococcic infections such as in dermatophytosis (but not on the latter itself). Occasional good results have been attained in sycosis vulgaris, secondary dermal infections, varicose ulcers and eczema, infectious eczematoid dermatitis complicating chronic eczema and industrial dermatoses, with general criterion of use failure of the condition to respond to other therapeutic measures.

Care must be exercised to avoid hypersensitivity and sensitization. The latter will cause violent reactions if oral administration follows. The chief danger of sensitization lies in its lasting effect. This may endanger the patient later in life by prohibiting sulfonamide

treatment of such a condition as penumonia or a bacteremia. Treatment should never be extended for more than five days.

Complete debridement and cleanliness are prerequisite to local sulfonamide treatment, as the drugs are less effective and are inhibited in the presence of pus, exudate, bacterial and tissue decomposition products.

Oil-in-water emulsion bases are the best bases for local administration of sulfonamides. Greases, vanishing creams or heavy creams and other bases are unsatisfactory for a number of reasons. Powders and lotions may be used in some cases, but are unsatisfactory in staying power.

Sulfathiazole is apparently the drug of choice, because of little or no absorption with its use, as well as maximum effectiveness against infection. The smaller the crystals employed, the more effective the results, thus the rather extensive use of microcrystals prepared by supersonic vibrations. Sodium salts are probably not as satisfactory, since they are more soluble, higher in pH and consequently more irritating. The sulfonamides are in general bacteriostatic and under some conditions bactericidal. Adequate professional supervision must be exercised over the topical administration of sulfonamides.

Marfanil (Sulfabenzamine)

Considerable research work has been successfully carried on in the United States and the United Kingdom on the various sulfonamides and penicillin in the treatment of a wide variety of infections. The development of a sulfonamide effective against the anaerobic bacteria, *Clostridium welchii,* that cause gas gangrene in infected wounds, often necessitating amputation, has not been realized. These anaerobic bacteria are prolific in the soil of France and thus have represented a major threat to military successes in that area. In the period since 1941 the Allies have read German reports on experiences in wound surgery with a substance which apparently was an ideal local antiseptic. Domagk, discoverer of Prontosil and Prontosil Album, is credited with its discovery. This chemical was called by them "Marfanil", "Marfanil Prontalbin" or "Mesudin". In the interim the English captured enemy medical supplies among which was included this drug. It was found to be a homologue of sulfanilamide, known chemically as 4-amino-methylbenzene-sulfonamide.

This drug is an improvement on other sulfonamides in that it has the advantages of being effective in the presence of *p*-amino-benzoic acid and in the presence of pus and body fluids. This is highly important, as the other sulfonamides are inactivated in the presence of either. The recommendation has been made that this drug be given in conjunction with penicillin, and the results are predicted as superior to therapy with either sulfonamides or penicillin alone.

Within the last month there appeared a release on the preparation and pharmacological testing of this same chemical by one of our leading manufacturers. It is apparently to be known under the trademark of "Sulfamylon," when released for general use.

The field of chemotherapy is not the only field of chemical interest reflecting recent trends in medical science. Synthetic replacements for the alkaloids have also given evidence of striking value.

Dibutoline

Dibutoline is one of a new class of chlorine-like esters recently synthesized by Sean and co-workers. For routine ophthalmoscopic examination and cycloplegic refraction the new compound has advantages over homatropine and other drugs of atropine series. Action of the new drug is short; consequently, visual disability, particularly mydriasis, is less prolonged than when homatropine is used for routine examinations. The effect of dibutoline on the ciliary body and iris develop and wear off simultaneously, while iris effects of the atropine series are considerably more intense and prolonged than cycloplegia. Undesirable systemic effects from ocular administration of dibutoline are negligible, even in children. The new drug has a disadvantage in that repeated administrations at short intervals are apt to produce a transitory superficial punctate disturbance of the corneal epithelium. In the treatment of anterior segment inflammation, the new compound has the advantage of having a bactericidal or a bacteriostatic action which is lacking in the atropine series.

Synthetic Quinine

The war has brought about a great many scientific discoveries due to the stoppage of supplies of various drugs from Axis-held territory. One of the first shortages of drugs in the war was that of quinine. A large quantity of quinine was collected from the pharma-

cists of the United States, but this did not for long remedy the critical situation.

In May of this year the synthesis of quinine was announced by Woodward and Doering. Although a far cry from commercial production this synthesis is an important step forward. In addition, the method produced an optical isomer of quinine which may prove of medical value.

The synthetic antimalarials quinacrine hydrochloride (atabrine) and pamaquine naphthoate (plasmochin) are now being produced in tremendous quantities. An announcement was recently made by the Board for the coordination of Malarial Studies of the National Research Council stating, in essence, that quinacrine is as good or even better than quinine in both the suppression and treatment of malaria. It was, however, the opinion of the Board that quinine and totaquine would be required in large quantities for use by civilian populations in occupied territory wherein the immediate dissemination of information concerning the use of quinacrine was not practical.

Other chemical developments are worthy of mention. Among these are the newer germicides based on an entirely new concept of germicidal action, and the newest insecticide, "D. D. T.," which was until recently a "hush hush" military secret.

Cationic Germicides

Hand in hand with the progress in the sulfonamides has gone the advance in a new class of germicidal agents. These new agents are known as cationic "surface active agents" or invert soaps, in that they are cation active, i. e., positively charged. Domagk, the original discoverer of sulfanilamide, is also credited with the first technical development of these compounds as bactericides. Chemically they are quaternary ammonium compounds.

The cationic germicides now available commercially include "Ceepryn," "Phemerol" and "Zephiran," and others are being developed. These germicides possess the advantages of being soluble in water and having a very low toxicity. They act on bacteria without discoloring the skin, with little irritant, toxic or caustic effects and can be used in high dilutions.

A *surface active agent* is defined as a substance which decreases or otherwise modifies the interfacial tension. Those agents which possess surface activity require only small concentrations to be effec-

tive. Most substances of this type are anion active, such as sodium lauryl sulfate. Surface active agents are often added to germicides to reduce the surface tension and thus expedite penetration of the wound, thus these new antiseptics are unique in that they are both bactericidal and also greatly lower interfacial tension. The cationic agents are more readily absorbed by bacteria than are the anionic agents, since bacteria are probably negatively charged. The sorption of such agents on bacteria causes an inhibition of the latter's action presumably by interfering with the functioning of its cell membrane.

By the sorption of the cationic agents the normal absorption of nutritional cationic substances necessary to the bacteria is prevented.

The cationic germicides have found application as general antiseptics for preoperative use and in gynecology, dermatology and ophthalmology.

The main disadvantage of such agents is their incompatibility with soap, an anionic agent. Soap must be thoroughly washed off the skin before using a cationic germicide. Even in high dilutions the cationic agents are excellent detergents and therefore use of soap can be eliminated.

The acridine dyes being positive are therefore compatible. Blood proteins inactivate cations, therefore it is impossible to employ the cationic germicides systemically. Fortunately they are not inactivated by the presence of serum in wounds where they have found wide application.

"D. D. T."

Yesterday, a military secret; today, the subject of great industrial expansion to meet critical war needs, a new chemical insecticide appears to hold great promise for civilian use in the future.

D. D. T., known chemically as dichlor-diphenyl-trichlorethane, was first developed in Germany in 1874. In 1939 in Switzerland, it appeared under the name of Gesarol and then became known domestically as Neocid. In the search for a replacement for the scarce rotenone and pyrethrum the Army came upon this compound. D. D. T. enters the body of the insect through the chemotactic sensorial organs found at the tip of the tarsi. Irritation and death occur practically instantaneously through its effect on the insect's nervous system.

The interest in D. D. T. today, however, rests chiefly in its significance with human infestations and insect invasions of human habitations.

The chemical, in insecticidal quantities, is reasonably nontoxic to humans, although excessive amounts (as compared to ordinary usage) administered orally are toxic. Solutions in oil are absorbable dermally, requiring care on the part of users of the product. It is not toxic via inhalation, but should not be allowed to contaminate or to fall upon foodstuffs.

D. D. T. has already proven of great value in the frontal military areas where mosquito eradication or body louse removal are factors in the control of malaria and typhus fever. Dusted into the clothing in the form of a powder, a single application provides anti-louse protection for a month. Soldiers are provided with the powder in shaker-top cans. Laundering of clothes does not appreciably diminish its effect. More important to us for the future are its civilian uses, for when a solution is sprayed in a room, it provides freedom from flies and mosquitoes for a month, without further use being necessary. Its value in other insect eradication has been recently reported.

However, biological and chemical therapeutic agents do not in themselves represent the only significant developments in recent months.

Pyrogens

The industrial purification of water by the use of base exchanges is quite common. Synthetic organic resins developed for use by the U. S. Navy to eliminate saline ions of sea water, to make the latter potable for those on life-rafts and life-boats, have a new peace-time application. Investigation has revealed that these resins can be employed to prepare pyrogen-free water without need for the distillation procedure which is necessary in the permanganate process now official in the National Formulary. This represents a most striking development, and indicates but another peace-time application of a War-encouraged discovery. Like many others, the peace-time use of this development may prove even more significant than the life-saving importance of its present use. This trend is also amply evidenced by blood plasma and its derivatives.

Blood and Its Fractions

Blood and its fractions have played a great part in the medical and pharmaceutical history of the War. A number of new developments have arisen as a result of the emergency use of human fluids.

The value of plasma in the treatment of shock has been adequately proven by war-time need. Its usefulness in civilian practice will be considerable even if not quite so extensive. The value of the by-product red cells in various technics of surgery and wound healing has but lately become recognized. In the near future it may assume great proportions.

If the processing of plasma were carried out only for the purpose of obtaining serum albumin, the latter's drawbacks and inadequacies would dissuade any general interest in its as a commercial peacetime product. However, the various fractions obtained from plasma in the process of obtaining serum albumin give considerable promise of yielding therapeutic agents which may revolutionize civilian medical practice in the post-war period. These are "fibrin foam" and "fibrin film," normal measles immune serum globulin, and other valuable agents. Present methods of development have been standardized, and clinical evidence is piling up. The future value and use of human blood and its fractions in general practice seems assured.

In addition to separating the various fractions of blood and determining their usefulness, much work has been done in the search for a plasma substitute. Only recently a specially prepared gelatin has been approved as the only substance thus far tested which gives evidence of possessing usefulness in this direction.

The field of therapeutic importance of tomorrow lies with the amino acids. The surface has, literally, only been scratched.

Amino Acids

It has been demonstrated that certain amino acids are essential to human growth, maintenance and physiologic well being. Some proteins fail to provide these essential amino acids, which are lysine, tryptophane, histidine, phenylalanine, leucine, isoleucine, threonine, methionine, valine and arginine. The non-essential acids include glycine, alanine, serine, norleucine, aspartic acid, glutamic acid, hydroxyglutamic acid, proline, hydroxyproline, citrulline, tyrosine and cystine. The observations of various workers in this field served as a guide to focus attention upon the significance of the quality of food proteins in respect to their amino-acid content, rather than the quantity of the protein.

Rose has defined an essential amino acid as one which cannot be synthesized by the animal body at a rate commensurate to meet its de-

mands for normal growth. In the group listed, arginine holds a unique position in that it can be synthesized by the animal organism, but only at such a rate as to provide 70 per cent to 80 per cent of the growth obtained when it is included in the diet.

However, the caution has been sounded not to conclude that the remainder of the protein molecule is of no value in nutrition.

Recent studies have revealed that age, species and degree of intestinal activity have an influence on the essentiality of the amino acids. For instance, adult rats are able to synthesize arginine rapidly enough for their needs, whereas young rats cannot. Mammals are able to synthesize sufficient aminoacetic acid, whereas chicks cannot do so. Histidine, essential to growth in rats, is not necessary to humans.

A further need for preformed amino acids is demonstrated when succinylsulfathiazole is adminstered. This drug inhibits intestinal bacteria, and when this occurs young rats were found to cease growing.

Intravenous injection of protein hydrolysates, by eliminating the processes of digestion and absorption, offers a physiological method of dealing with the nutrition of human subjects in a wide variety of pathological conditions in which oral feeding is impossible, difficult or ineffective. After surgical procedures, hemorrhage and burns, in which the demand for protein is greater than normal, the digests can be used effectively either alone or as supplements to the proteins of orally ingested food.

Recently Jennard has announced the development of a type of photometer which will enable physicians to determine very quickly whether the patient has a protein or amino-acid deficiency. At the present, complex physiological tests are the only means of such determinations.

There are commercially available several amino-acid preparations. Without doubt these will be improved upon or added to in the near future, as scientific knowledge of the field of amino acids expands.

Endocrines

During the past six months progress in endocrine therapy has not been outstanding. The most promising development has been the use of thiouracil in thyrotoxicosis. There have been different opinions regarding exophthalmic goiter, particularly in regard to its ultimate etiology. Removal in part of the gland is the accepted treatment, but

is not the ideal method. Toxicological tests of other drugs revealed that the thyroid gland secretion may be controlled pharmacologically. Various workers have found that different drugs (including some of the sulfonamides and phenylthiourea) caused thyroid hypertrophy in experimental animals. It is believed that these drugs prevent the formation of the thyroid hormone.

Lack of thyroid hormone will stimulate the pituitary to produce its thyroid stimulating hormone, thereby causing a hyperplastic gland. In this manner, hypothyroidism in the presence of a hyperplastic thyroid is explained. The ability to prevent the formation of thyroid hormone suggested that a drug of this type may offer a means of controlling hyperthyroidism.

A drug of low toxicity was required, and investigation of a large number of compounds resulted in the use of thiouracil. In many instances thiouracil has caused a current clinical remission of the disease which was maintained as long as therapy was continued. The size of the goiter decreased in most cases.

Even the basic elements themselves have not been without study in recent months.

Tantalum

A current advance in the field of surgery has been the use of tantalum, the seventy-third element of the periodic series, occurring in Group V. It is employed in plates and in threads. It has found application due to the discovery that it is biologically inert. It is resistant to all body fluids, and when used to repair bone fractures or to close wounds, it produces no foreign body reactions. This "foreign body reaction" is an overgrowth of tissue, due to the presence of metallic and other foreign substances, and it is well-known to the surgeon and histologist. In bone repair, when tantalum is employed, a normal bone growth without the characteristic callous occurs. A fine bluish-white film develops, starting at the edges of the metal, gradually covering it. This film is probably collagen; bone growth follows naturally after this primary growth.

Muscular cells are said not to attach themselves to any foreign substances. However, with tantalum fibroblastic cells have been found to affix themselves to it with subsequent tissue attachment.

Fine tantalum wire is used in neurosurgery. Tantalum foil is employed to prevent adhesions and fixation in brain operations and as cuffs in the repair of nerves and tendons.

Conclusion

In conclusion, it must be acknowledged that this review has of necessity touched upon only a few of the high spots of the medical and pharmaceutical advances of the past year. Certain trends are quite evident.

The emphasis upon chemotherapy, and upon specific therapeutic agents to treat a pathologic condition, is paramount. Equally important is a greater realization that the boundaries of medical and scientific knowledge are at present still quite limited, and that much of value lies beyond present understanding. That there will be a great adaptation of war medicine into civilian practice is certain. The therapeutic advances that will result are probably even beyond conjecture.

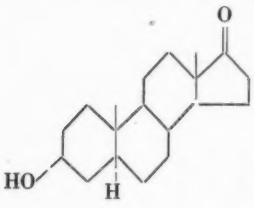
It is quite important that we realize the new role that will be held by Pharmacy and the pharmacist. The poly-scientific aspect of these newer trends indicates clearly that the pharmacist of the future will not be merely a technician, concerned solely with dispensing, but more probably a scientist whose chief role is the preparation and supplying of products, the scientific nature of which is so complex that the physician who employs them must of necessity rely upon his pharmacist for the technical knowledge and guidance required to use them properly and effectively.

THERAPEUTICALLY USEFUL ANDROGENS

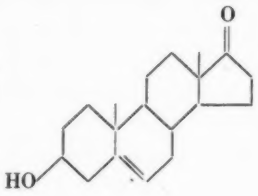
By Ralph I. Dorfman, Ph.D.*

Introduction

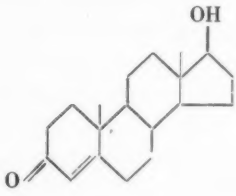
ALTHOUGH many attempts were made to correct the effects of decreased testicular secretion in men since the days of Brown-Sequard (1), it is only within the past 9 years that efficient therapy has been made available. The work of Butenandt and Tscherning (2) which yielded two pure androgens from normal men's urine, androsterone and dehydroisoandrosterone, was the first important advance in this field. Within a year, David et al.(3) isolated a third androgen from bull testis, testosterone, which is the most active androgen thus far isolated. The structure of this testis hormone was established by partial synthesis from cholesterol. To date, David's isolation remains the only reliable report of the isolation of an androgen from testis tissue. Although testosterone has been shown to undergo conversion in men to androsterone (4), (5), a normal urinary metabolite, no direct evidence is yet available that testosterone is produced by human testis.



Androsterone



Dehydroisoandrosterone



Testosterone

Physiological Considerations

The testis is known to have a dual function, that of spermatogenesis and the second the production of an internal secretion by the

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interstitial cells. The results of castration in mammals help to illustrate some of the physiological effects of the androgenic hormone. It is convenient to classify castrates into two groups: those in whom castration has occurred before puberty, and those in whom the testes were removed after sexual maturation.

In the prepuberal castrate, the genitalia remain small and underdeveloped, the long bones of the limbs show extraordinary length with a delay of epiphyseal union. The beard contains only fine hair and the voice retains a high pitch. Muscular development is usually retarded. The accessory sex organs such as the penis, seminal vesicles, prostate and preputial glands remain undeveloped. Postpuberal castration shows a somewhat different picture. The accessory sex organs undergo involution but do not go back to the immature state. Voice changes do not occur and some measure of sexual desire may persist.

Testosterone and methyltestosterone, the two androgens which have proved to be valuable in the treatment of castrate and eunuchoid individuals, show profound physiological activity. These androgens are capable of reversing the changes observed in prepuberal and postpuberal castrates. Thus the accessory sex organs may be stimulated to approach the physiological status of the normal man. The secondary sex characteristics such as voice changes, beard, and libido can be influenced.

The two androgens, testosterone and methyltestosterone, also show profound effects in women. Depending upon the dosage of androgen administered and the phase of the menstrual cycle, various effects have been observed. The physiological effects following the administration of these androgens in women as listed by Salmon (6) are as follows:

(a) The next menstrual period is suppressed or delayed by 2 or more weeks.

(b) The endometrium, at the end of about 4 weeks, is found to show absence of the secretory pattern, hypoplasia or atrophy.

(c) The vaginal smear presents a picture characteristic of estrogen deficiency (disappearance of the cornified squamous epithelial cells and their replacement by the small atrophy cells and leucocytes).

(d) The vaginal mucosa shows involutional changes similar to postmenopause atrophy. At the same time, the glycogen in the desquamated vaginal epithelial cells is strikingly reduced or disappears completely.

(e) The normal contractions of the fallopian tubes and uterus are suppressed.

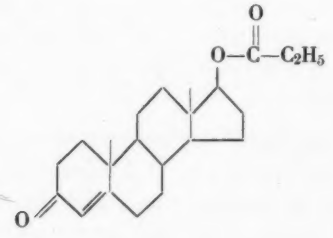
The administration of androgens during the first 2 weeks of the menstrual cycle eliminates the next menses probably by suppression of the anterior pituitary. Further, progesterone production is also depressed as seen by the fact that excretion of urinary pregnanediol (a metabolite of progesterone) is definitely decreased. If the amounts of androgens administered to women are sufficiently high, other changes may occur in women such as hypertrichosis, voice changes, and enlargement of the clitoris. These effects may persist for some months after large doses (7).

The bulk of evidence indicates that testosterone or methyltestosterone can inhibit lactation (8). In both men and women, androgens have been shown to have specific effects on general metabolism. Chief effects are retention of N and P and gain in body weight. These effects have been noted in patients suffering from Cushing's disease (9), in Addison's disease (10), in Simmond's disease (11), in normal men and women as well as hypogonadal men and women (12), (13).

Chemical and Physical Properties

Two related substances have been shown to be of clinical value: testosterone propionate and methyltestosterone.

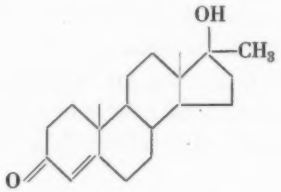
Testosterone propionate: M. P. 121° C.



Testosterone propionate is a white crystalline solid insoluble in water but soluble in alcohol, ether, and vegetable oils such as olive oil, cottonseed, sesame, etc. Partial synthesis has been carried out from cholesterol, in small yields. The propionate is most often employed therapeutically since the ester has a more prolonged action than the free compound. When equal doses of testosterone and testosterone propionate are administered and the effect on the rat prostate and seminal vesicles observed, it is found that the action of the propionate persists 3 to 4 times longer. Further, under these conditions, the propionate also elicits a greater maximum response. The ester has the further advantage of being more soluble in vegetable oil.

Since the amounts of active material are relatively large, it may be possible to quantitate the amount of testosterone propionate by direct isolation and identification. Work on such a method is now in progress in this laboratory. No official method of standardization has been adopted.

Methyltestosterone: M. P. 165-6° C.



This steroid is related to testosterone, being the 17-methyl derivative. It is a white crystalline substance insoluble in water but soluble in alcohol, ether and vegetable oil. Partial synthesis has been accomplished from cholesterol. It is more active than either testosterone or testosterone propionate by the oral route, but less active than testosterone propionate by intramuscular injection.

Recent work in this laboratory has indicated the feasibility of assaying methyltestosterone preparations by direct isolation and identification of the active substance from commercial tablets. As yet, no official method of standardization has been adopted.

Clinical Uses in Men

In patients with bilateral orchidectomy or eunuchoidism, androgenic therapy is often of value. Those patients who show signs of fatigability, nervous instability, and sexual incapacity are often aided

by adequate dosages of either testosterone propionate or methyltestosterone. In long continued cryptorchidism, where decreased production of androgens may be noted (14), androgen therapy is indicated. In certain types of male sterility, the administration of androgens may result in increasing the number of mature, viable and motile spermatozoa. Dosage is an important factor since larger doses may actually cause a decrease in the number of normal spermatozoa.

The efficacy of androgenic therapy in cases of impotence is still a debatable point. In one report, on 12 cases, no improvement was noted (15), but the dosage was relatively small or the interval between injections long, or both. Others have reported favorable results (16).

A climacteric in men seems to occur in at least a small percentage of men with advancing age. Evidence has accumulated that in at least some of these cases, androgen therapy produced improvement in muscle tone, improved appetite and general well-being (17).

Some favorable reports have been published on the control of symptoms and signs of prostatic hypertrophy. When the proper dose of androgens was administered, decrease in the amount of residual urine and in nocturia have been noted as well as less perineal discomfort and increase in general mental and physical well-being. Androgenic therapy has been suggested as a valuable adjunct to surgery in prostatic hypertrophy cases where there is a deficiency of testicular secretion (18).

Favorable results have been reported in conditions of gynecomastia. Three-quarters of a series of patients treated with either testosterone propionate or testosterone acetate have shown either partial or complete regression (19).

Clinical Uses in Women

The use of androgens to control the menopausal syndrome has been suggested (20). The latter workers reported excellent results in all of 15 menopausal patients, including 2 surgical castrates. Evidence has been presented for use of androgens for the inhibition of lactation, excessive uterine bleeding and dysmenorrhea.

Commercial Preparations

Table I is a summary of the various forms of testosterone propionate and methyltestosterone available for therapeutic use. The

TABLE I

COMMERCIAL PREPARATIONS OF ANDROGENS FOR CLINICAL USE

Androgen	Intramuscular administration mg/cc. oil	Oral administration mg/tablet	Topical application mg/g. of ointment	Implantation mg/pellet	Sublingual administration mg/tablet	Firm*	Trade Name
Testosterone propionate	5, 10, 25	..	..	..	..	I	Perandren
Testosterone propionate	5, 10, 25	..	..	..	..	II	Neo-Hombreol
Testosterone propionate	5, 10, 25	..	..	..	..	III	Oreton
Testosterone propionate	..	..	..	75	..	III	Oreton-F
Testosterone propionate	..	..	2	..	..	I	Perandren
Methyltestosterone	..	..	2	..	..	II	Neo-Hombreol (m)
Methyltestosterone	..	..	2	..	..	III	Oreton-M
Methyltestosterone	..	10	..	..	..	I	Metandren
Methyltestosterone	..	10	..	..	..	II	Neo-Hombreol (m)
Methyltestosterone	..	10	..	..	..	III	Oreton-M
Methyltestosterone	..	..	..	..	5	I	Metandren

* I—Ciba Pharmaceutical Products, Inc.
II—Roche-Organon, Inc.
III—Schering Corporation.

substances are put up for 5 types of administration: intramuscular, oral, topical, sublingual and implantation.

For intramuscular administration, the preparations contain 5, 10 or 25 mg. of testosterone propionate per cc. of oil; for oral administration, methyltestosterone is marketed in 10 mg. tablets. Two of the firms use methyltestosterone, while the third uses testosterone propionate for topical application preparations. These preparations are prepared so that each gram of ointment contains 2 mg. of androgen. Commercially made pellets are now available for subcutaneous implantation. These pellets contain 75 mg. of testosterone. For sublingual therapy, a special tablet containing 5 mg. of methyltestosterone is made.

When long continued treatment is indicated, there is little doubt that the pellet implantation is the mode of choice (21), (22), (23), (24). The implantation of testosterone is at least twice as efficient as intramuscular injection as judged by weight of material required per day to produce good clinical results in hypogonadal men. When androgenic effects are desired for brief intervals as is the case in women, pellet implantation is contraindicated. In such cases, intramuscular administration or oral administration of proper androgen is indicated. Sublingual administration is being studied at the present time with some favorable results reported in the literature.

Summary

Testosterone propionate and methyltestosterone have proved to be therapeutically useful substances in the treatment of men showing signs of deficient testicular secretion as well as in selected conditions in women. Suitable commercial products are now available for administration by the following routes: intramuscular, oral, topical, sublingual and implantation.

The physiological effects and clinical uses of the androgens are briefly discussed.

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ECONOMIC REALITIES

THE NATURE OF TRADE

By Karl Scholz, Ph. D.*

A BASIC characteristic of industrial organization in our economy is division of labor. Every working individual ordinarily engages in a single occupation, or performs only one or a limited number of tasks, and trusts that others, likewise specializing, will provide him with the countless commodities and services he does not produce himself. Such division of labor, to be beneficial to all concerned, necessitates exchange or trade, which takes place in either local, national of international markets.

The true nature of trade, growing out of division of labor, is not fully understood by the lay public. Many popular misconceptions will have to be cleared away, before economic realities will prevail concerning trade.

Fundamentally, all trade consists of buying and selling, rather than, as popularly interpreted, of either buying or selling. A moment's reflection should make it clear that it is impossible to buy without selling and to sell without buying. All trade is in the nature of two-way traffic, rather than one-way traffic, such as either charity or robbery. The fact that most trade is carried on with the aid of money and credit has beclouded our thinking concerning trade. We do not ordinarily speak of buying money when we sell goods, or of selling money when we buy goods. Yet even a credit transaction involves the sale of a promise to pay in return for the purchase of goods.

Since it is impossible to sell without buying, and vice versa, it becomes apparent that in every trade or exchange there must be at least two buyers and two sellers, since each dealer functions in a dual capacity, as both buyer and seller. Furthermore, a person who en-

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gages in trade gains from the transaction in his capacity as buyer rather than as seller. Our economy rests largely on the assumption that individuals, whether they be business or professional men, farmers or day-laborers, looking out for their own best interests, will seek to get as much as possible for what they sell, and give no more than necessary for what they buy. What they buy or receive when they trade measures their gain or income, while what they give up expresses their cost or outgo. The difference between gain and cost is the net gain growing out of trade. If we fully grasped the significance of the elementary economic truth that in trading we gain in the capacity of buyers rather than as sellers, we might be inclined to take a somewhat different attitude toward trade, particularly toward international trade.

Fundamentally, such trade does not differ significantly from either local or nation-wide trade. If, as buyers, always looking out for our own economic interests, we wanted to maximize our gain and minimize costs, we would buy where we could buy cheaply, whether at home or abroad, assuming equal quality products. Yet the popular belief prevails that we, the people, gain by keeping out cheap foreign goods, with the aid of protective tariffs and other artificial trade restrictions. Any suggestion by economists that all such trade barriers tend to diminish the opportunities to realize the full benefits of division of labor, by narrowing the markets for the exchange of goods, is commonly viewed as purely theoretical and academic. Yet it is a basic economic truth that any man-made restrictions placed on buying and selling decrease the opportunities for the full realization of the gains resulting from division of labor. Because of the popular illusion that trade consists of selling, we are only too willing to encourage the sale of our surplus products in world markets, even if we have to give foreigners the money with which to buy them, as we did unwittingly during the New Era of the twenties. But we manifest great reluctance to buy outside of the United States, believing that we would be the losers if we allowed the importation of cheap goods from abroad.

The chief reason for much of the confusion of thought concerning the nature of trade may be found in the fact that we fail to distinguish between commercial transactions and economic transactions. Commercial transactions consist of the sale of goods for money or promises to pay—credit—and the transactions are viewed as com-

pleted when the seller has gotten his money for the sale, or the buyer has paid his bill. If, for example, the seller of the goods draws a draft on the buyer and sells it to the bank, he may get his money even before the buyer has paid his bill. But all such financial and commercial transactions are really only partial or incomplete economic transactions. Trade, in the economic sense of the word, consists of an exchange of commodities and services for commodities and services. Money and credit are merely convenient devices to facilitate trade, but the sale of goods for money, the commercial transaction, becomes an economic transaction only as the money thus acquired is exchanged for other goods. In the final analysis, the only thing money is good for is to get rid of it to buy the things that really satisfy human wants. If, therefore, we wanted to promote our best economic interest, we should focus our thinking more on buying cheaply, rather than merely on selling dearly. It is in the capacity of buyers that we gain from trade, and not as sellers. This elementary economic truth is fundamental to an understanding of the real nature of all trade growing out of division of labor, and based on freedom of choice and action.

INFORMATION OF VALUE TO THE GENERAL PUBLIC REGARDING POLIOMYELITIS

Pharmacists should be in a position to provide patrons with accurate advice on poliomyelitis at this season of the year. The following suggestions from the National Foundation for Infantile Paralysis will be helpful wherever outbreaks of the disease have occurred:

1. During an outbreak of infantile paralysis be alert to any early signs of illness or changes in normal state of health, especially in children. Do not assume that a stomach upset with vomiting, constipation, diarrhea, severe headache or signs of a cold and fever are of no importance. These may be among the first symptoms of infantile paralysis. All children and adults sick with unexplained fever should be put to bed and isolated pending medical diagnosis.

2. Don't delay calling a physician. Expert medical care given early may prevent many of the crippling deformities. Proper care from the onset may mean the difference between a life of crippling and normal recovery.

3. Today there is no known prevention or protection against infantile paralysis. All that can be done is to provide the best possible care. Your doctor, your health officer and your local Chapter of The National Foundation for Infantile Paralysis can and will do everything in their power to see to it that your community is ready to meet an epidemic.

4. Observe these simple precautions:

(a) Avoid overtiring and extreme fatigue from strenuous exercise.

(b) Avoid sudden chilling such as would come from a plunge into extremely cold water on a very hot day.

(c) Pay careful attention to personal cleanliness, such as thorough washing before eating. Hygienic habits should always be observed.

(d) If possible avoid tonsil and adenoid operations during epidemics. Carefuly study has shown that such operations, when done during an epidemic, tend to increase the danger of contracting infantile paralysis in its most serious form.

(e) Use the purest milk and water you can. Keep flies away from food. While the exact means of spread of the disease is not known, contaminated water and milk are always dangerous and flies have repeatedly been shown to carry the infantile paralysis virus.

(f) Do not swim in polluted water.

(g) Maintain community sanitation at a high level at all times.

(h) Avoid all unnecessary contact with persons with any illness suspicious of infantile paralysis.

PROPOSED ADDITIONS TO THE U. S. P. XIII

The Subcommittee on Scope of the United States Pharmacopœia has released the following list of proposed additions for inclusion in the U. S. P. XIII:

Adrenal Cortex Injection (in oil and aqueous)
Aluminum Phosphate Gel
Aminopyrine Tablets
Amino Acids Mixture (oral)
Amphetamine
Amphetamine Sulfate and preparations
Anhydrohydroxyprogesterone
Anhydrohydroxyprogesterone Tablets
Apomorphine Hydrochloride Tablets
Bacterial Vaccine from Cholera Vibrio
Bacterial Vaccine from Plague Bacillus
Benzyl Benzoate and Lotion
Calamine, Prepared
Calamine Lotion
Coal Tar
Coal Tar Ointment
Copper Citrate
Copper Citrate Ointment (Ophthalmic)
Desoxycorticosterone Acetate
Desoxycorticosterone Acetate Injection (in oil)
Desoxycorticosterone Acetate Pellets
Dicalcium Phosphate (Dibasic Calcium Phosphate)
Diethylstilbestrol Suppositories
Digitoxin
Digitoxin Injection
Digitoxin Tablets
Digoxin
Digoxin Injection
Digoxin Tablets
Diodrast
Diphtheria Toxoid, Tetanus Toxoid Alum Precipitated, Combined
Diphtheria Toxoid, Tetanus Toxoid Fluid, Combined
Doryl and Preparations (tablets and injection)
Epinephrine Injection (in oil suspension)
Estradiol Benzoate Injection (in oil)
Estradiol Suppositories
Estradiol Tablets
Estrone Injection
Estrone Suppositories
Extralin
Gas Gangrene Antitoxin

Gas Gangrene Antitoxin Polyvalent
Helium
Heparin
Hexylresorcinol Capsules
Hydrophilic Ointment Base
Isopropyl Alcohol
Lactate-Ringer's Solution
Lanatoside C
Lanatoside C Injection
Lanatoside C Tablets
Mecholyl Bromide
Mecholyl Bromide Tablets
Mecholyl Chloride
Mecholyl Chloride Injection
Methyl Testosterone
Methyl Testosterone Tablets
Morphine Injection
Naphuride (Bayer 205) and Injection
Natural Estrogens
Natural Estrogens Capsules
Natural Estrogens Injection (in oil and aqueous)
Natural Estrogens Suppositories
Natural Estrogens Tablets
Neo-Synephrine Hydrochloride and preparations
Nicotinamide Injection
Papaverine Hydrochloride and Injection
Penicillin
Pentothal Sodium
Pitressin Tannate Injection (in oil)
Pregnancy Urine Gonadotrophin
Progesterone
Progesterone Injection (in oil)
Protamine Zinc-Insulin Injection
Purified Protein Derivatives of Tuberculin
Riboflavin Injection
Sodium Ascorbate
Sodium Ascorbate Injection
Sodium Morrhuate
Sodium Morrhuate Injection
Sodium r-Lactate Injection
Sodium R-Lactate Ringers Solution
Sulfamerazine
Sulfamerazine Sodium Sterile
Sulfamerazine Tablets
Testosterone Propionate
Testosterone Propionate Injection (in oil)
Tetanus Gas Gangrene Antitoxin
Thiamine Hydrochloride Injection
Typhus Fever Vaccine
Vinethene
Yellow Fever Vaccine
Zephiran Chloride and preparations

SELECTED ABSTRACTS

Experimental Clostridium welchii Infection: IV. Penicillin Therapy. L. R. Hac. *J. Infect. Dis. 74,* 164 (1944); through *U. S. Naval Med. Bull. 43,* 300 (1944). Mice were infected experimentally with *Cl. welchii* by the intramuscular route, and the results obtained in over 1,100 animals treated with penicillin were compared with those observed in simultaneous experiments with other chemotherapeutic agents. Additional experiments on a small series of guinea pigs confirmed the observations made on mice.

The smallest dose of penicillin administered (5 Oxford units) was equal in its protective effect to the largest dose of the most effective sulfonamide. Continued penicillin therapy was superior to a single dose of the drug, since the former gave better protection and also resulted in smaller lesions at the site of inoculation; e. g., 7 injections of 25 units each protected 96 per cent of the animals, whereas 1 injection of 500 units protected 98 per cent.

Delaying the start of penicillin therapy was less hazardous than is the case with the sulfonamides, although the percentage of survivors was appreciably lowered by a delay of 3 hours.

Penicillin was much more effective than all other agents tested in localizing the infectious agent, in minimizing the effects of toxemia and tissue damage, and in speeding repair. The lesions at the site of inoculation healed within ten to eighteen days under penicillin therapy, but required from twenty-two to thirty-six days when the sulfonamides were used. Additional therapy, however, is needed to check the initial rapid invasion by *Cl. welchii,* with the production of early edema and late destructive lesions.

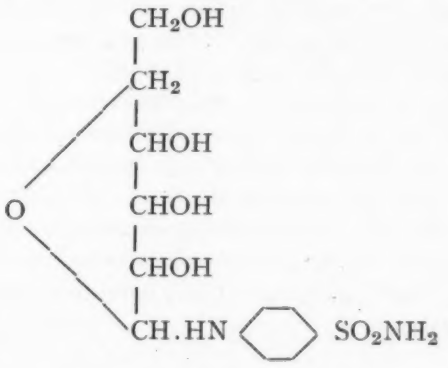
Adequate surgery combined with chemotherapy is more effective than the latter alone.

Use of Nonabsorbable Sulfasuxidine in Extensive Burns. C. W. Tennison. *Surgery 15,* 332 (1944); through *U. S. Naval Med. Bull. 43,* 310 (1944). In a series of third-degree burn cases in which

from 20 to 45 per cent of the body surface was involved, sulfasuxidine was found to facilitate earlier multiple grafting operations, without the loss of any grafts. Up to 25 gm. of the drug were dusted on the affected areas, followed by a pressure dressing of boric acid ointment.

No toxic effects were observed, and the blood concentration of the drug was always found to be zero. Marked reduction in the temperatures of patients with high fever was noted. Since it was not necessary to change dressings oftener than from four to eight days, this mode of treatment proved to be better tolerated by the patients than certain other methods.

Glucostreptocide. A. P. Lubinin. *Pharm. J. 99,* 89 (1944). Glucostreptocide is prepared by the condensation of glucose and sulfanilamide, and has the following structure:



Experiments performed on white mice indicated that this product has only about one-fourth the toxicity of sulfanilamide, a characteristic importance in the saturation type of anti-bacterial therapy. The compound was tried clinically on 30 patients ranging in age from 18 to 46. Inasmuch as the molecular weights of glucose and sulfanilamide are almost equal, the dosage administered was twice the usual dose of the latter. The first group of 7 cases received 6 gm. daily; the second group of 16 cases, 3 gm. daily; the third group, 1.5 gm.

daily. The drug was given every six hours to patients of the first group, and every three hours to those of the other two groups.

The optimum dosage was found to be 6 gm. daily. No toxic effects were observed. Cases with bubo and balanitis cleared up without surgical interference.

The Analysis of B. P. C. Pastilles. N. Evers and W. Smith. *Pharm. J. 99,* 63 (1944). Pastilles are made in machines which expel a quantity of liquid mixture through rows of jets into starch molds. The authors investigated the variations caused by (a) difference in the size of jets or in the amount delivered by the pumps, (b) the position of the jets in the row, and (c) external factors acting on all jets throughout the run, e. g., the height of the liquid in the feed tank.

It was found that for pastilles weighing 25 to 30 grains the variation from the mean weight of the majority was $\mp$ 6 per cent. The results indicated that variations in weight may be caused by (a) a trend towards lighter pastilles through the run of a batch, and (b) differences in the amount delivered by individual jets.

The authors also investigated the analytical procedure for pastilles of the Codex, all of which have a glycogelatin base. They recommend hydrolysis of the gelatin by boiling with dilute alkalis or mineral acids as the best method for removing the base. Methods of analysis were developed for the various types of ingredients; the technics were checked by the analysis of a batch of glycogelatin pastilles containing a known amount of each ingredient. Good agreement was obtained in the majority of cases.

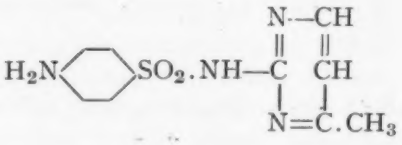
Use of Sulfapyrazine in Infants and Children. H. L. Barnett, A. M. Perley, G. B. Forbes and D. Goldring. *Am. J. M. Sc. 206,* 599 (1943); through *U. S. Naval Med. Bull. 43,* 244 (1944). Sulfapyrazine, which chemically is 2-sulfanilamidopyrazine, was administered orally to children with various types of mild or moderately se-

vere infections. The following dosage scheme was adhered to as closely as possible: 0.1 gm. per kg. body weight for an initial dose, followed by 0.2 gm. per kg. every 24 hours in 4 divided doses. Blood levels of the free drug were determined at intervals during the course of several days' treatment.

The average blood level of the drug for the patients under 2 years of age was 3.3 mg. per 100 cc., and 5.3 mg. per 100 cc. for those over this age. Lower blood levels in infants on proportionate doses have been noted with other sulfonamides. The sulfapyrazine blood levels observed were comparatively uniform in this series of cases. High blood levels can be rapidly attained and maintained by the subcutaneous administration of the sodium derivative. With comparable blood levels, the therapeutic effectiveness of sulfapyrazine appeared to be equal to that of any of the commonly used sulfonamides.

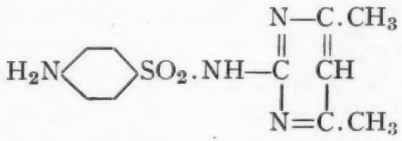
New Sulfonamides: A Survey. T. D. Whittet. *Chem. Products 7,* 64 (1944). *Sulfadiazine.* Against infection by the streptococcus, pneumococcus, meningococcus, gonococcus, and Friedlander's bacillus, this drug is similar in its action to sulfathiazole; it has been claimed to be more effective than the latter in staphylococcal infections, though this point requires further study.

Sulfamerizine (or sulfamerazine). This drug is monomethyl sulfadiazine:



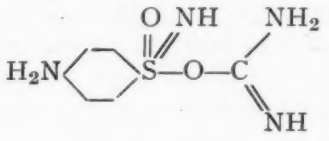
In activity and toxicity it is similar to sulfadiazine, but may be given in smaller doses, since it is more quickly absorbed and is excreted very slowly. The high solubility of the acetylated form reduces the danger of renal complications.

Sulfamezathine (formerly sulfamethazine). This is the dimethyl derivative of sulfadiazine:



Sulfamezathine is useful in the treatment of pneumococcal, meningococcal, haemolytic streptococcal infections and *B. coli* infections of the urinary tract. Its action against the staphylococcus has not been determined. The solubility of the drug and its acetyl derivative is greater than that of either of the drugs previously mentioned.

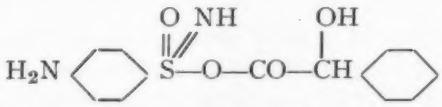
Sulfonamido-Urea. The observation that the administration of urea with a sulfonamide produced a marked increase in the bacteriostatic properties of the latter, as well as removing the inhibitory effect of *p*-aminobenzoic acid and methionine, led to the synthesis of sulfonamido-urea, the enol form of which has the following structure:



This drug is useful in all cases in which the organism is sulfonamide resistant. It is believed that such resistance is due to the acquired ability of the organism to synthesize abnormally large amounts of *p*-aminobenzoic acid.

Succinyl Sulfathiazole. This drug was introduced under the trade name "Sulfasuxidine" in the United States, and is now produced in England as "Colistatin." It is but very slightly absorbed from the gastro-intestinal tract, a fact which makes the drug useful in treating intestinal disorders such as bacillary dysentery and also for pre-operative use to minimize the danger of contamination and secondary infection.

Sulfanilyl-Mandelate. Both mandelic acid and sulfanilamide have been used in the treatment of *B. coli* infections of the genito-urinary tract. The new compound sulfanilyl-mandelate combines the action of both drugs, since upon hydrolysis in the body it liberates these substances. The enol form of the compound has this structure:



Although the therapeutic activity of sulfanilamide is independent of pH, mandelic acid requires a pH of 5 for maximum effectiveness. *In vitro* studies of sulfanilyl-mandelate indicate that in the presence of water or other solvent it assumes the tautomeric keto phase, which facilitates the splitting of the amido linkage. The amount of mandelic acid liberated is sufficient, under normal conditions, to maintain the required urinary pH.

Sulfanilamide is more readily absorbed and excreted when combined with a water-soluble acid radical. Its combination with mandelic acid is indicated in most infections of the genito-urinary tract; it has low toxicity, and it does not greatly disturb the acid-base balance of the body.

Thiourea as Protective Agent for Vitamin C. E. Kawereau and W. R. Fearon. *Sci. Proc. Roy. Dublin Soc. 23,* 171 (1944); through *Analyst 69,* 221 (1944). An investigation of a large number of substances to determine their capability of protecting vitamin C from oxidation in the presence of copper revealed that thiourea possesses this property to a marked degree. This compound was found to have low toxicity when administered to human subjects; it is excreted unchanged by the kidneys. Before thiourea can be used on the large scale for this purpose, long-term experiments will be necessary.

It was noted that boiled vegetable extracts possess similar protective powers which, in certain instances, suggest the presence of specific stabilizers. It is possible that the latter may be thiols, since cabbage was found to contain an unidentified thiol compound. Potato juice yielded an active distillate on boiling.

SOLID EXTRACTS

Brief Reports on New Items of Interest

"Heart worms" frequently cause disease and death among dogs. A recent news item described the complete cure of Admiral Byrd's famed dog, Rickey, which was suffering from this disease. The drug used was "Fuadin," an organic antimony compound, which is used widely in certain tropical diseases such as bilharziasis and kala azar. The name "Fuadin" was coined using King Fuad's name, since his support of the trial of this drug in Egypt led to its present widespread use in the tropics.

AJP

The use of sulfonamides in the treatment of poliomyelitis is not only valueless, but evidence is accumulating that it may even do real damage by producing an extension of the paralysis or by making it more intense. Penicillin likewise does no apparent good, but it has not been observed to do harm.

AJP

The use of ultra-violet light in the diagnosis of certain diseases and diseased states of the skin and scalp was recently described by a group of physicians of the Bellevue Hospital, New York. It is particularly useful in detecting cases of *tinea capitis* and in examining large numbers of children in the school, where such outbreaks occur.

AJP

It is interesting to note the radical decline in the number of scientific papers now appearing on subjects dealing with the sulfonamides, and the concurrent increase in the number of reports on penicillin. This swing of the pendulum of popular interest is indeed significant.

The War Department has given some preliminary information about a newly developed odorless, greaseless, non-sticky oil treatment for hospital floors, blankets and beddings that prevents the spread of disease by these natural carriers. The new oil treatment confines the various disease-producing organisms so securely that they cannot spread through the atmosphere, the bacterial count dropping in one instance from 3,500 to 350 per cubic foot of air. Blankets so treated are also warmer. War-time security measures have not allowed the divulgence of the formula except that mineral oil and oleic acid are among the ingredients.

AJP

Man's normal life span could be and may be raised to 130 years according to Dr. Theodore G. Klumpp. Since in the animal kingdom the life span of a species is five or six times longer than its period of maturation, such a figure is biologically sound. We know but little concerning those factors responsible for man's decline in health. One fact is irrefutable and that is the observation that obesity definitely shortens life expectancy. The effects of other factors such as diet, vitamins, sunshine, alcohol, etc., are not fully established.

AJP

The question, "What pure organic compound is prepared in the largest quantity in the United States?" rarely receives the right answer. Substances usually mentioned because they are known to have numerous uses in industry are: aniline, phthalic anhydride, phenol, formaldehyde, glycerol and isopropyl alcohol. Actually sugar possesses this distinction, the 1939 production being 13,349,998,000 pounds. Chemists are inclined to overlook this substnce since it is so common, just as they possibly overlook the possibilities of syntheses using sugar as the starting point.

Most of us may not consider tuberculosis a very interesting or threatening disease, but, since "Pearl Harbor," it has killed 145,000 civilians in the United States alone.

AJP

Penicillin is giving very promising results in the treatment of syphilis. It appears likely that this drug may prove to be the best antisyphilitic yet discovered. The problem at present is twofold: first to determine the optimum dosage level, and second, to learn if the rapid clinical and serologic improvement already noted is an indication of permanent cure. Not all cases of syphilis respond favorably to penicillin therapy as it is used today, but a fairly high percentage show rapid improvement.

AJP

The first reported case of penicillin dermatitis has been put in print. It concerns a doctor who experienced a skin eruption due to contact with penicillin through his duties in preparing solutions of the drug. When he refrained from working with penicillin, the dermatitis disappeared.

AJP

Hay fever sufferers in a number of cities, of which Philadelphia and Cleveland are examples, may look to certain of their newspapers for a daily pollen count during the season. Not that this helps their affliction any, but it may be some satisfaction to know that the count for the day is 108 grains of ragweed pollen per square inch, while the previous high for that particular day was 92 in 1936, and the average is 25.

BOOK REVIEWS

Textbook of Pharmacology (for Students in Pharmaceutical Institutes). By Prof. M. P. Nicolaev. Authorized for publication by the "NARKOMZDRAV" of the U. S. S. R. (Russia). Published by the "Government Publishing House for Medicinal Literature" or "MEDGIZ" (Gosudarstvenoyo Izdatelstvo Meditsinskoi Literatury). Moscow, 1943. 364 pages, Cloth-bound, with paper cover. 94 drawings in the text. Price: U. S. A., about $2.50; Russia, 14 Rubles 50 Kopeks.

This textbook of pharmacology is written entirely in Russian and begins appropriately by first defining the word "Pharmacology." The subject matter in this text is divided into two sections, namely: (1) "General Pharmacology," and (2) "Classified or Specialized Pharmacology."

The section on "General Pharmacology" discusses this subject under the following topic sub-titles:

1. A Short Historical Review of the Origin and Development of Pharmacology.

2. The Subject Matter and Problems of Pharmacology.

3. Modes of Action of Medicinal Substances.

4. Dependence of Pharmacological Action on the Nature of the Medicinal Substance.

5. Biological Standardization of Medicinal Substances.

6. The Relation of the Action of a Drug to its Dose.

7. The Dependence of the Action of a Medicinal Substance upon its Chemical Composition.

8. The Dependence of Pharmacological Action upon the Condition of the Organism.

9. The Dependence of the Action of a Medicinal Substance upon the Channels of its Administration.

10. The Actions of Combined Medicinal Substances.

11. The Fate of the Medicinal Substances in the Human Organism.

12. Manifestation of Symptoms in Continued Administration of Medicinal Substances.

13. Established First Aid Measures in Cases of Poisoning.

14. Classification of Medicinal Substances for Studying Their Pharmacological Action.

In order to facilitate the study of medicaments in this book, and to keep the groupings intact, the author has resorted to a "mixed classification" of drugs, pharmaceuticals and medicinal compounds. This systematization is accomplished by grouping the medicinals according to their mode of action and their chemical composition. The second section of this book, dealing with "Classified or Specialized Pharmacology" embodies these groupings. The material covered in this section falls under the following group titles:

1. Substances Acting Preeminently upon the Central Nervous System.
   - A. Substances Depressing the Central Nervous System.
   - B. Substances Stimulating the Central Nervous System.

2. Substances Acting Preeminently upon the Peripheral Nervous System.
   - A. Substances Acting on the Sensory Nerves.
   - B. Substances Acting on the Vegetative Nervous System.

3. Substances Acting Preeminently upon the Heart and Blood Circulatory System.

4. Substances Having a Preeminent Local and Peripheral Action.

5. Disinfectants and Parasiticides.

6. Antipyretic Substances.

7. Compounds of Metals and Metalloids.
   - A. Alkali Salts and Alkaline Earth Metals.
   - B. Acids and Alkalies.
   - C. The Oxygen Group.
   - D. Halogens.

E. Sulfur and its Compounds.

F. Heavy Metals.

G. Metalloids.

8. Preparations of Vitamins, Ferments, Hormones and Tissue Substances.

A. Vitamin Preparations.

B. Ferment Preparations.

C. Hormone Preparations.

D. Preparations of Tissue Products.

This volume is written in a professional style of Russian and presupposes that the reader has a thorough understanding of chemistry, pharmacy, and physiology. The text is amply augmented by many graphs, tables, drawings and diagrams which serve as aids in clarifying the topics discussed. Chemical formulas are stated for all chemical medicinals and numerous structural formulas are presented for the many complex organic compounds dealt with. This book contains an introduction, a table of contents, a Latin Subject Matter Index, and a Russian Subject Matter Index.

In strict adherence to modern Russian pharmaceutical practice, which contends that the Russian pharmacist should be familiar with official and proprietary preparations of the entire world, this work on pharmacology goes on to discuss such drugs as Baume Bengue, Tyrothricin, Cibalgin, Isacen, Insulin, Aspidium, Cyclopropane, Lu-in-pen, Avertin, etc., etc.

The doses of all medicines included in the Seventh Edition of the Government Pharmacopœia U. S. S. R. are covered as well as those of many non-official proprietary preparations. The highest dose that may be safely administered within a twenty-four hour period is designated within parentheses, while the largest single dose is given outside of the parentheses. For example: Pure Codeine 0.05 Gm.—(0.20 Gm.).

In spite of the fact that Professor Nicolaev's "Textbook of Pharmacology" is printed on wood pulp paper it embodies a wealth of information which may not ordinarily be found in a single volume of similar nature. For those who possess a thorough understanding of Russian and an advanced Russian medical vocabulary, this work should prove to be of interest to the students of Russian pharmacy

and medicine. It is also an excellent reference text for the pharmacologist, hospital pharmacist, and physician who may, at some time, be called upon to investigate, compound, or prescribe Russian prescriptions.

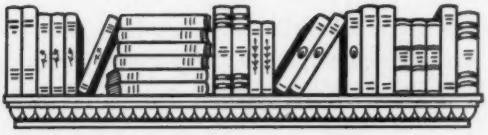
EDGARD YAN ALLEN.

Cumulative Index for Volumes I to VI of the Chemical Formulary. By H. Bennett. Chemical Publishing Co., Inc., Brooklyn, N. Y. 1944. 164 pages. Price: $4.00.

To those who are frequent users of the Chemical Formulary this volume will satisfy a long-felt need. The first cumulative index to these volumes covers I to III, but with the three additional volumes a new one was needed.

The index is comprehensive in nature, covering all the formulæ included in the six volumes. It is extensively cross-indexed to facilitate ease of reference, giving both volume and page number.

M. O. HOLLAND.



American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

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